MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE

Hilton Gaithersburg Hotel, 620 Perry Parkway, Gaithersburg, Maryland, 20877

Friday, September 23, 2011

The meeting was convened at approximately 8:00 a.m.

Members Present (Voting)
Geoff Rosenthal, M.D., Ph.D. *(Chair)*
Kathleen Motil, M.D., Ph.D.
Alexander Rakowsky, M.D.
Michael Reed, PharmD., FCCP, FCP
Kenneth E. Towbin, M.D.
Jeffrey Wagener, M.D.

Temporary Voting Members (Voting Consultants)
Frank Balis, M.D.
Jeffery Brinker, M.D.
Amy Celento, B.S. (*Consumer Representative)*
Rick Chappell, Ph.D.
Carl D'Angio, M.D.
Leon Dure, M.D.
Marilyn Eichner (*Patient Representative*)
Keith Kocis, M.D., M.S.
Jonathan Mink, M.D., Ph.D.
Jose Romero, M.D.
Allen J. Vaida, Pharm D., FASHP
Michael White, M.D., Ph.D

Executive Secretary
Walter Ellenberg, Ph.D.

U.S. Food and Drug Administration (FDA) Participants
Debra Boxwell, Pharm.D.
Yodit Belew, M.D.
Grace Chai, Pharm.D.
Judith Cope, M.D., M.P.H.
Wiley Chambers, M.D.
Susan K. Cummins, MD, MPH
Virginia Elgin, M.D.
Laura Governale, PharmD, MBA
Norman Herskowitz, MD, Ph.D.
Chris Jones, Pharm.D.

Alyson Karesh, M.D.
Suhail Kasim, M.D.
Jenny Chih-Hsin Liu, RN, BSN, MSN
Markham Luke, M.D.
Lisa Mathis, M.D.
Dianne Murphy, M.D.
Carol Pamer, RPh, M.S.
Andreas Pikis, M.D.
John Sapirstein, MD
Kelley Simms, PharmD
Tom Smith, M.D.
Dale Tavris, MD, MPH
Amy Taylor, M.D.
Carolyn Vaughan, BSME
Ron Yustein, M.D.

Open Public Hearing Speakers

A written comment was summarized on behalf of Jean Public.
Diana Zuckerman, Ph.D., President, National Research Center for Women & Families gave a slide presentation regarding ongoing safety concerns with the use of atypical antipsychotics in the pediatric population.

Presentations

Welcome and Introductory Remarks
Geoffrey Rosenthal, MD, PhD Chair of Pediatric Advisory Committee Director of Pediatric & Congenital Heart Center Executive Director, Critical Care Services University of Maryland Medical Center Hospital for Children

Walter Ellenberg, PhD Designated Federal Official, Pediatric Advisory Committee Office of Pediatric Therapeutics, Office of Special Medical Programs, OC, FDA

Agenda Overview
Dianne Murphy, MD, Director Office of Pediatric Therapeutics OC, FDA

Melody Transcatheter Pulmonary Valve and Ensemble Delivery System
Carolyn Vaughan, BSME, Office of Device Evaluation, CDRH, FDA
John Sapirstein, MD, Office of Device Evaluation, CDRH, FDA
Jenny Chih-Hsin Liu, RN, BSN, MSN, Office of Surveillance and Biometrics, CDRH, FDA
Dale Tavris, MD, MPH, Office of Surveillance and Biometrics, CDRH, FDA
Susan K. Cummins, MD, MPH, FAAP, Office of the Center Director, CDRH, FDA

Sponsor Presentation
Dr. Thomas Armitage, Vice President of Clinical Affairs Medtronic, Inc

Melody TPV Questions and Recommendations
Susan K. Cummins, MD, MPH, FAAP, Office of the Center Director, CDRH, FDA

Abbreviated Presentations: Akten (lidocaine hydrochloride), Navstel (balanced salt ophthalmic solution with hypromellose, dextrose, and glutathione), Triesence (triamcinolone acetonide injectable suspension),
Judith Cope, MD, MPH, Office of Pediatric Therapeutics OC, FDA

Modified Abbreviated: Famvir (famciclovir), Videx EC (didanosine), Ziagen (abacavir sulfate), Zomig Nasal Spray (zolmitriptan)
Judith Cope, MD, MPH, Office of Pediatric Therapeutics OC, FDA

Topamax (topiramate) Standard Review of Adverse Events
Virginia Elgin, MD, Pediatric & Maternal Health Staff, Office of New Drugs, CDER, FDA

Retrovir (zidovudine) Standard Review of Adverse Events
Alyson Karesh, MD, Pediatric & Maternal Health Staff, Office of New Drugs, CDER, FDA

Retrovir (zidovudine) Medication Errors Review
Carol Pamer, RPh, MS, Division of Medication Error Prevention and Analysis, OSE, CDER

Levaquin (levofloxacin) for Anthrax Post- exposure Standard Review of Adverse Events
Amy Taylor, MD, Pediatric & Maternal Health Staff, Office of New Drugs, CDER, FDA

Informational Update of Kaletra (lopinavir/ritonavir)
Debra Boxwell, PharmD, Office of Surveillance and Epidemiology, CDER

PAC Member Designated Review
Dianne Murphy, MD, Director Office of Pediatric Therapeutics, OC, FDA

Adjournment
Geoffrey Rosenthal, MD, PhD Chair of Pediatric Advisory Committee

Summary of FDA Questions, Committee Discussion, Vote and Recommendations

Melody Transcatheter Pulmonary Valve and Ensemble Delivery System

Questions to the Committee

- *FDA will continue its standard ongoing safety monitoring of the Melody TPV. Does the Committee concur?*

- *The number of Melody TPV devices distributed per year (524 in 2010) is below the ADN of the Melody TPV (2,996 for 2010). Does the Committee think that the exemption on the limit for profit making remains appropriate?*

Committee Discussion
The committee discussed the HDE and profit-making waiver for Melody TPV. The committee asked how the device is used as an adjunct to surgery and what the purpose of this device is in relation to the treatment of pulmonary valve insufficiency. FDA responded that this device does not replace surgery but rather extends the time periods between to surgical reinterventions. The committee asked if the presence of the device hampers/hinders surgical reintervention. FDA responded that there is no safety signal from surgeons that the presence of the valve hampers

surgical re-interventions. The committee expressed concern with 3 subjects in the post-approval study who were lost to follow-up. The committee requested to know whether the last observation of the 3 subjects was accounted for in the data analysis, and whether the last observation for those subjects would be carried through in future analyses.

The committee noted that patients who received the device in the U.S. appeared to have been less sick than patients receiving the device in Europe. The committee asked what comparators were used in the post-approval studies. FDA responded that the post-approval studies used performance goals as comparators. The committee expressed concern regarding the lack of historical controls or any controls in the post-approval study. The committee discussed the 3 cases of endocarditis. FDA reviewed the source data from these 3 cases and concluded that the events were not definitively caused by the device.

The committee discussed the off-label use of the device in other cardiac valves. The sponsor responded that their estimates from implant registration forms indicate that 94% of Melody TPV devices are used in the pulmonic position and 6% are not. The committee stated that off-label use of the device should be tracked. The committee discussed that the device needed further improvements, including possible techniques to reduce hyperplasia around the valve and stent. The committee also discussed the sponsor's training and preceptor program with the device as there were 2 Medical Device Reporting (MDRs) indicating Melody TPV being deployed in the right ventricle of 2 pediatric patients. The sponsor responded that each physician undergoes rigorous training including on-site, multi-step, didactic training at the Medtronics training center in Minnesota; simulators are used, each physician is challenged by experienced preceptors and a Medtronic representative attends each Melody TPV implant case.

Stent fractures were discussed at length by the committee. The committee discussed the nature of the device fractures. The device exists in a hostile environment withstanding various pressures. The rate of stent fractures is high but the sponsor reported that approximately half of fractures are clinically silent. Clinicians have developed innovative methods to decrease the rate of stent fractures such as "pre-stenting" prior to Melody TPV placement.

Committee Vote

- Fourteen (14) committee members concurred with returning the device to routine MDR and literature review, with the request that FDA should bring the product back to the PAC if a signal is identified. Also, the product should return to the committee after the post-approval studies are completed.
  Three (3) committee members did not concur.

- Seventeen (17) committee members unanimously agreed that the exemption on the limit for profit making remains appropriate at this time.

Abbreviated Presentation: Navestel (balanced salt ophthalmic solution with hypromellose, dextrose, and glutathione)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Vote

- Seventeen (17) committee members unanimously agreed to continue ongoing safety monitoring of these products.

Abbreviated Presentation: Akten (lidocaine hydrochloride)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Vote

- Seventeen (17) committee members unanimously agreed to continue ongoing safety monitoring of these products.

Abbreviated Presentation: Triescence (triamcinolone acetonide injectable suspension)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Vote

- Seventeen (17) committee members unanimously agreed to continue ongoing safety monitoring of these products.

Modified Abbreviated Presentation: Ziagen (abacavir sulfate)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Discussion

The committee discussed if the decreased use of Ziagen (abacavir sulfate) was due to an issue with safety or efficacy of the drug in pediatrics. FDA responded that the decreased use is most likely related to treatment guidelines recommending that this drug is not the preferred drug in

this population. A recent report suggested that Ziagen use was associated with an increased risk of cardiovascular disease. FDA has not made this recommendation but rather it was driven by treatment guidance.

Committee Vote

- Sixteen (16) committee members agreed to continue ongoing safety monitoring of these products. One committee member abstained from voting.

Modified Abbreviated Presentation: Famvir (famciclovir)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Discussion
The committee inquired about how data on newborns was captured with this drug. The data captured is only when a child was given the drug directly. In utero use information is captured in pregnancy registries however Famvir does not have a pregnancy registry.

Committee Vote

- Sixteen (16) committee members unanimously agreed to continue ongoing safety monitoring of these products. One committee member was recused from voting.

Modified Abbreviated Presentation: Videx EC (didanosine)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Vote

- Fifteen (15) committee members unanimously agreed to continue ongoing safety monitoring of these products. Two committee members were recused from voting.

Modified Abbreviated Presentation: Zomig Nasal Spray (zolmitriptan)

Question to the Committee

- *FDA recommends returning this product to its standard ongoing safety monitoring. Does the committee concur?*

Committee Vote

- Fifteen (15) committee members unanimously agreed to continue ongoing safety monitoring of these products.

Two committee members were recused from voting.

Standard Presentation of Adverse Events: Topamax (topiramate)

Question to the Committee

- *The FDA will continue to monitor for any new bleeding events. Does the Committee concur?*

Committee Discussion:
The committee discussed potential gaps in the current labeling regarding potential safety concerns related to weight loss, bone mineralization and bleeding complications. For example, the risk for epistaxis in the label does not convey a life-threatening bleeding risk. Emphasis should be placed on monitoring for new bleeding events. Also, the members stated that they thought the current label underestimates the cognitive adverse effects of the drug.

The committee raised serious concerns with the extent of Topamax use in the pediatric population for migraine. Although not approved for treatment of migraines in pediatrics, 80% of use in the 10-16 year old age group is for this off-label indication. The committee strongly recommended that the findings from the adolescent study of migraines be added to the current label. Also, the members stated that they thought the current label underestimates the cognitive adverse effects of the drug.

FDA is requesting a one-year active control study with this drug to evaluate safety concerns regarding metabolic acidosis, renal stone formation, bone mineral density and development (height, weight, and pubertal). FDA stated that when labeling changes are completed this product will again trigger the PAC process for the committee's review of Topamax.

Committee Vote

- Ten (10) committee members disagreed with the FDA plan to continue to monitor for bleeding events without additional labeling changes.
  Four (4) committee members agreed to continue to monitor for bleeding events.
  One committee member abstained from voting.
  One committee member was recused from voting.
  One committee member was absent from the vote.

Standard Presentation of Adverse Events: Retrovir (zidovudine)

Question to the Committee

- *Please discuss the following options:*
  1. Return to routine monitoring without any labeling changes
  2. Changes to the label should reflect the recommendations from the Division of Medication Errors Prevention and Analysis
  3. Return to routine monitoring after changes have been made
  4. Provide a follow-up report of medication errors after changes have been made

Committee Discussion:
The committee praised the FDA staff for their work in identifying medication errors issues. Dosing changes from 50mg/5ml to 10 mg/ml will make a big difference in reducing medication errors. The committee thought that these dosing errors are not specific to Retrovir but could also be applied to drugs with similar concentration directives. The committee discussed how the drug was administered using a syringe provided by nurse or pharmacist.

Committee Vote:

- Sixteen (16) committee members voted unanimously that changes to the label should reflect the recommendations from the FDA's Division of Medication Errors Prevention and Analysis. They agreed to return Retrovir to routine monitoring after changes have been made. Also, the committee agreed that FDA should provide a follow-up report on medication errors after changes have been made.
  One committee member was absent from the vote.

Standard Presentation of Adverse Events: Levaquin

Question to the Committee

- *FDA recommends continuing routine, ongoing post-marketing safety monitoring Does the Committee concur?*

Committee Discussion
The committee inquired why dosing is provided in the label when there is no pediatric indication. Ciprofloxacin is the only other fluoroquinolone with a pediatric indication. All reported pediatric use of Levaquin is off-label. The dosing in the existing label is indicated for use as an alternative product in the stockpile to be used in an emergency response.

Committee Vote

- Fifteen (15) committee members agreed to continue ongoing safety monitoring of these products.
  One (1) committee member disagreed with the plan to continue routine ongoing post-marketing safety monitoring and wanted to address off-label use of this product in the pediatric population.
  One committee member was absent from the vote.

Informational Update of Kaletra (lopinavir/ritonavir)

The committee commended FDA's action on the safety signal identified in neonates receiving the Kaletra formulation containing polyethylene glycol and ethanol. The committee discussed the possibility of adding a Black Box Warning to the label for Kaletra regarding the safety signal in neonates. The committee also stated that FDA should review all drugs containing polyethylene glycol in its formulation in early infancy. The committee stated that this is an example of why drugs need to be developed specifically for children, especially in HIV where there is not a big market however, there is a big need.

PAC Member Directed Abbreviated Review (PDAR) for mandated pediatric focused safety reviews

Question to the Committee

- *Are PAC members willing to try this new process?*
- *Are there suggestions to improve the process?*
- *Are there suggestions on how to identify Abbreviated Reviewers other than to distribute the work evenly?*

Committee Discussion

The committee discussed the frustration of the ever increasing conflict of interest process related to competing products. This process has resulted in limited availability of experts in various fields.

The committee stated that the new process would allow committee members time to focus on products that have public health issues. The committee expressed concerns related to the division of labor across committee members when assigning the abbreviated product review.

Committee Vote

- Thirteen (13) committee members agreed to FDA plans for a PAC Member Directed Abbreviated Review (PDAR).
  One committee member abstained from voting.
  Three committee members were absent from the vote.

The meeting adjourned at approximately 4:05 p.m.

Please see transcript for details

I certify that I attended the September 23, 2011 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

/s/	/s/
Walter Ellenberg, PhD.	Geoffrey Rosenthal, M.D. Ph.D.
Executive Secretary	Chair